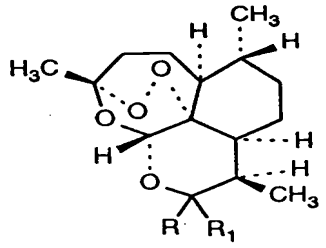
and a compound of the formula



(II),

wherein R and R_1 together represent oxygen or one of R and R_1 individually represents hydroxy or C_1-C_6-alkoxy and the other represents hydrogen or a pharmaceutically acceptable salt thereof,

the combination being synergistic and the combined amount of the compounds administered being an antimalarially effective amount.--

R E M A R K S

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Initially, Applicants wish to take this opportunity to express their appreciation to the Examiner for granting an interview to Applicants' attorney concerning the application on August 18, 1992. During this interview the issues outstanding in connection with this application were discussed and the substance of the interview is summarized in the EXAMINER INTERVIEW SUMMARY RECORD prepared by the Examiner at the time of the interview. The paper prepared by the Examiner is believed to accurately summarize the substance of the discussion at the interview with the exception that the rejection of the claims based upon the

prior art Wang et al. and Sethi et al. references was also discussed. The understanding arrived at at the interview was that the instant response would be presented by Applicants for the careful consideration of the Examiner.

The specification is amended to correct a minor typographical error at page 2.

The claims of the application are amended by cancelling, without prejudice to the subject matter involved, claims 11 to 16 and replacing them by newly formulated claims 17 to 25. These new claims are drafted in a manner to most adequately define the subject matter of the present invention and in a manner believed to place this application in immediate condition for allowance. Substantial changes are effected in the claims and thus it is believed that significant discussion of the amended claims for the benefit of the Examiner's consideration is warranted.

Claim 17 is the broad composition claim now presented and claim 25 is the broad method of use claim. These new claims effectively replace former claims 11 and 16 respectively.

In new claim 17, the language has been changed to specify that the composition comprises a synergistic anti-malarial effective amount of a combination of the compound benflumetol of the formula specified and a compound of formula (II) as defined and pharmaceutically acceptable additives. The introductory language now employed in the claim is believed to most adequately define the subject matter of the invention. Thus, the combination of active ingredients is functionally defined as being one which is synergistic. Further, the amount of the combination is functionally defined as being an anti-malarial effective

amount. This is, of course, in direct accord with the disclosure of the application as filed.

It is further believed that this definition is preferable to the previous definition in which each of the active ingredients is specified as a synergistically effective amount. The word "synergistic" has meaning with respect to the combination rather than with respect to each of the individual components.

In the original claim 1 of the application, the Applicants functionally defined the components as "a synergistically effective amount" without specifying the ratio of the components.

In the first Official Action, the Examiner took the position that this phrase was indefinite and rejected the claims as failing to adequately define the invention under the provisions of 35 U.S.C. 112.

In presenting claim 11, Applicants further specified the ratio of the active ingredients as being from 1 to 10 parts by weight of the compound benflumetol for each part by weight of the compound of the formula (II).

However, based upon the data set forth in the accompanying Declaration Under Rule 132 of Dr. Walther H. Wernsdorfer, to be discussed in more detail later herein, it is apparent that that specific ratio is unduly narrow to protect the subject matter of the present invention.

Thus, in the newly presented claims 17 and 25, Applicants have returned to the original functional definition to specify a synergistic combination. In this respect,

Applicants respectfully submit that this definition, in functional terms, is neither indefinite nor unduly broad and thus clearly should be permitted. In this respect, Applicants direct the attention of the Examiner to the case of Ex parte Ponsford, decided by the USPTO Board of Appeals on March 25, 1982 and reported in 575 PTCJ A-13 of April 15, 1982. In that opinion, Examiner Goldstein took the position that there is nothing inherently indefinite in the use of functional limitations. He stated that the expressions "synergistically effective amount" and "antibacterially effective amount" both have art-recognized meanings and are particularly definite when read in the light of the disclosure. This is, likewise, the situation in the present case and the Examiner is respectfully requested to recognize the propriety of the language now employed in the claims.

Furthermore, in claim 17, the compounds of the formula (II) have been more specifically defined within the scope of the original disclosure. This has been done in order to bring the claimed subject matter into closer accord with the scope of the data now being presented to more clearly establish the synergistic action of the combination. This aspect of the matter will be discussed in more detail later herein.

As indicated above, claim 25 is the generic method of use claim. The language of this claim accords generally with that of the newly presented claim 17. Claim 17, however, requires that the active ingredients be combined in the single composition. The language of claim 25 has, however, been drafted somewhat more broadly in order to permit the active components to be separately administered as well as through a single composition. It will be apparent to one skilled in the art that the synergistic action of the combination can be achieved through the separate

administration of the active components as well as from administration in a single composition. Thus, Applicants are entitled to such breadth of protection.

Claim 18 is directed to the composition further more specifically defining the compounds of the formula (II).

Claim 19 further more specifically defines the compound of the formula (II) as artemether.

Claims 20 and 21 are dependent, respectively, upon claims 17 and 19 and more specifically define the weight ratio of benflumetol to the compound of formula (II). The specific weight ratio range specified is drawn from the data of the Declaration of Dr. Wernsdorfer which establishes this range as being synergistic. In recognizing the support in the Declaration for this range, certain points need to be considered by the Examiner.

In the first place, in the Wernsdorfer Declaration, there is a reverse order of agents as compared to the claims. Thus, Dr. Wernsdorfer stated the ratios in his Declaration in terms of artemether (A):benflumetol (B) while the claims, from the beginning have stated the ratio in terms of benflumetol:the compound of formula (II). It is the hope of the Applicants that this will not be unduly confusing to the Examiner.

Secondly, Dr. Wernsdorfer has stated the ratio in terms of their relative molar ratios rather than as a pure weight ratio as in the specification and claims. The molecular weight of benflumetol (I):$C_{30}H_{32}Cl_3NO$ is 528.35 g and the molecular weight of the representative compound of formula (II) artemether:$C_{16}H_{26}O_5$ is 298 g. This means that the

molecular weight of benflumetol is 1.8 times higher than the molecular weight of artemether or, the molecular weight of artemether is only 56% of the molecular weight of benflumetol.

In the Declaration, wherein artemether (II) is mentioned first and benflumetol (I) in the second place, a broad molar range from 1.0:1.0 to 1.0:30.0 has been documented and supported by the tests set forth. This corresponds to a weight range of from 1.0:1.8 to 1.0:54.0 which has now been demonstrated to be synergistic.

From this discussion the Examiner will readily appreciate the basis for the weight ratio range which is set forth in new claims 20 and 21.

The Applicants recognize, of course, that this express weight ratio range is not expressly set forth in the specification as filed. It must be recognized, however, that this range is within the range of the broad "synergistically effective" disclosure of the present application as filed. Applicants respectfully submit that they are entitled to present claims specifying this range even though the range is not expressly stated in the application as filed. This principle is well stated in cases such as In re Wertheim, 191 USPQ 90, and In re Johnson, 194 USPQ 187.

Claims 22, 23 and 24 specify the particular weight ratio of benflumetol to artemether as expressly disclosed in the specification and set forth in former claims 13, 14 and 15 respectively.

Based upon the foregoing remarks, Applicants respectfully submit that the claims as now presented are clearly supported by the application as filed and the patentability of the amended claims will be apparent from the remarks set forth herein.

The Examiner has rejected the claims as being anticipated under the provisions of 35 U.S.C. 102(a) by the WHO report (AR). This ground of rejection is deemed to be untenable and is thus respectfully traversed.

In rejecting the claims, the Examiner points out that it has not been established that the meeting referenced in the WHO report was a closed meeting and that the material disclosed or discussed therein was given in confidence. In order to establish this, Applicants are presenting the Declarations of Yiqing Zhou and Jiaxiang Shen. These Declarations clearly establish that the attendants at the meeting in question was very limited and that the data presented were presented on a confidential basis. It is believed, therefore, that in view of these Declarations, the Examiner will now reconsider and withdraw this ground of rejection of the claims.

The claims are further rejected as being unpatentable under 35 U.S.C. 102(f). The Examiner raises the question of whether the Applicants themselves invented the claimed subject matter. This ground of rejection is likewise deemed to be untenable and is respectfully traversed.

The initial point to be made in regard to this ground of rejection is that in filing the present application, the inventors have executed a Declaration stating that they

consider themselves to be the inventors of the subject matter of the present application. As the Examiner will appreciate, that statement by the inventors must be recognized by the Examiner in the absence of evidence to indicate that the inventors are not truly the inventors of the subject matter disclosed and claimed.

It is respectfully submitted that the WHO report cited by the Examiner does not constitute evidence to contradict this assertion by the Applicants.

In the first place, the indication in the WHO report to the effect that the combination of active ingredients is being administered orally in China as an antimalarial treatment does not provide any indication that this administration is by persons other than the inventors. For the position taken by the Examiner to have merit, the publication itself would have to provide some indication that other persons were performing the administration.

Secondly, the WHO report is a 1990 report and the Declaration of Mr. Zhou which is submitted herewith reveals that in 1989 Mr. Zhou was in possession of the subject matter of the present invention. This clearly antedates the date of the WHO report.

Thus, Applicants respectfully submit that the WHO report does not constitute evidence sufficient to support the position of the Examiner and, even if it did, the date is antedated by the Declarations submitted herewith. It is thus respectfully requested that the Examiner now reconsider and withdraw this ground of rejection.

Finally, the claims are rejected as lacking patentability under the provisions of 35 U.S.C. 103 over the Wang et al. and Sethi et al. references. This ground of rejection is likewise deemed to be untenable and is respectfully traversed.

In rejecting the claims, the position which the Examiner takes is that the references disclose the employment of the individual components in the treatment of malaria. It is urged that in view of this, it would be prima facie obvious to one of ordinary skill in the art to employ the combination in the treatment of malaria.

There is some question in the minds of the Applicants regarding whether the general proposition stated by the Examiner in rejecting the claims is valid. Thus, as a general proposition, Applicants question whether it can properly be said that merely because each of the individual components is known in the treatment of malaria, it would be prima facie obvious to the art-skilled to employ a combination of these materials in the treatment of malaria. Be that as it may, however, the Examiner appears to appreciate the basic proposition that if true synergistic action in the combination is established, any presumption of prima facie obviousness will be overcome. In the Official Action, the Examiner appears to question whether true synergism has been demonstrated.

In order to more clearly establish that true synergistic action exists, Applicants are submitting herewith the Declaration of Dr. Walther H. Wernsdorfer.

Dr. Wernsdorfer is one of the foremost experts in the world in malaria therapy. His familiarity with the subject matter to which the present application pertains is evident from the introductory portion of the Declaration submitted.

Dr. Wernsdorfer reports the results of extensive in vitro tests with various parasites and has compared the action of the individual agents artemether (A) - the compound of formula (II) wherein one of R and R_1 represents methoxy and the other represents hydrogen - and benflumetol of formula (I) as compared to combinations of those agents in different amounts. Again, the Examiner is reminded that the order of the agents stated in the Declaration is the reverse of the order stated in the claims.

Attention is particularly directed to Section 3, Conclusion. The combined effect is especially pronounced at EC_{99}. The concentration required for 99 % inhibition of parasite reproduction is 1/25 to 1/214 of the dose expected from mere additive activity. Such pronounced reduction of ECC_{99} is highly desirable for the following reason.

A growth inhibition of 99% of the isolates considerably diminishes or almost excludes the risk of regrowth of protozoae, for which malaria is notoriously known. Therefore, in order to be sufficiently effective, antimalarial agents are administered in dose amounts to achieve this essential 99% growth inhibition of the parasite. However, for many agents used in therapy, the dosages are too high to be physiologically acceptable since they tend to approach toxicological levels. A reduction of EC_{99}, especially as found according to the Declaration of Dr. Wernsdorfer, raises the physiological tolerability of a drug or drug combination and enables the physical to administer lower doses.

The EC_{50} and EC_{90} values represent concentrations wherein 50% and 90% respectively of the parasites are inhibited. It is understood that these values are insufficient to inhibit regrowth of protozoa. But, low EC_{50} and EC_{90} values are also indicative of good therapeutic activity especially when compared with those of other agents.

Applicants respectfully submit, therefore, that the Declaration of Dr. Wernsdorfer clearly establishes the synergistic effectiveness of the combination claimed and thus, the presumption of prima facie obviousness based upon the teachings of the cited references is clearly overcome and the rejection is untenable.

It is noted that the data set forth in the Wernsdorfer Declaration is specifically directed to the combination of artemether and benflumetol. On the other hand, certain claims of the present application are sufficiently broad to be inclusive of compounds of formula (II) in addition to artemether. This raises, of course, a question of whether the results set forth in the Declaration are commensurate in scope with the claims presented.

The Declaration of Dr. Wernsdorfer does, of course, clearly support patentability of synergistic mixture where artemether is present. Applicants respectfully submit that the inclusion of other derivatives within the scope of the claims is warranted in view of their close structural relationship and their identical utility as antimalarial agents.

All compounds covered by the scope of formula (II) have the identical structural backbone and the structural differences which still exist are caused by structural variation at the

same position of this structural backbone. The scope of formula (II) as specified in the generic claims herein is, therefore, quite limited. All derivatives covered by formula (II) have the central peroxo group in common which is believed to produce the antimalarial effect.

Applicants have disclosed an invention which is clearly broader than the single combination of benflumetol and artemether. Applicants should not be placed in a position where the claims of their invention are so limited as to enable others in the art to avoid the protection by merely employing other closely related materials. The results of the data with artemether are deemed to be representative and illustrative and to support the patentability of these closely related materials.

Based upon all of the foregoing amendments and remarks, Applicants respectfully submit that each of the rejections set forth against the present application has been overcome and that the application is now in condition for allowance; such allowance is solicited.

Respectfully submitted,

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August 27, 1992